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SPECIAL ARTICLE

International Myeloma Working Group Recommendations for the Treatment of Multiple Myeloma–Related Bone Disease

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ABSTRACT

Purpose
The aim of the International Myeloma Working Group was to develop practice recommendations for the management of multiple myeloma (MM) –related bone disease.

Methodology
An interdisciplinary panel of clinical experts on MM and myeloma bone disease developed recommendations based on published data through August 2012. Expert consensus was used to propose additional recommendations in situations where there were insufficient published data. Levels of evidence and grades of recommendations were assigned and approved by panel members.

Recommendations
Bisphosphonates (BPs) should be considered in all patients with MM receiving first-line antimyeloma therapy, regardless of presence of osteolytic bone lesions on conventional radiography. However, it is unknown if BPs offer any advantage in patients with no bone disease assessed by magnetic resonance imaging or positron emission tomography/computed tomography. Intravenous (IV) zoledronic acid (ZOL) or pamidronate (PAM) is recommended for preventing skeletal-related events in patients with MM. ZOL is preferred over oral clodronate in newly diagnosed patients with MM because of its potential antimyeloma effects and survival benefits. BPs should be administered every 3 to 4 weeks IV during initial therapy. ZOL or PAM should be continued in patients with active disease and should be resumed after disease relapse, if discontinued in patients achieving complete or very good partial response. BPs are well tolerated, but preventive strategies must be instituted to avoid renal toxicity or osteonecrosis of the jaw. Kyphoplasty should be considered for symptomatic vertebral compression fractures. Low-dose radiation therapy can be used for palliation of uncontrolled pain, impending pathologic fracture, or spinal cord compression. Orthopedic consultation should be sought for long-bone fractures, spinal cord compression, and vertebral column instability.

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INTRODUCTION

Multiple myeloma (MM) is an incurable plasma-cell malignancy,[1,2] despite the improvement in survival after the introduction of novel agents.[3,4] MM is characterized by osteolytic bone disease resulting from increased osteoclast activity and reduced osteoblast function.[5-7] Osteolytic lesions are detected in 70% to 80% of patients at diagnosis and increase the risk for skeletal-related events (SREs; pathologic fractures, spinal cord compression [SCC], requirement for surgery or palliative radiotherapy to bone).[8,9] SREs impair survival,[10] undermine quality of life (QoL),[11] and increase treatment costs.[12,13] Previous recommendations for the management of MM with bisphosphonates (BPs) have been compiled by several organizations[14-19] (Table 1), and the International Myeloma Working Group (IMWG) has also developed additional recommendations related to bone disease of MM and monoclonal gammopathy of undetermined significance (MGUS).[20-22] During the last years, several important studies have been reported in the field. The IMWG reviewed all available evidence; we provide below recommendations for the management of myeloma-related bone disease.

METHODOLOGY

An interdisciplinary panel of clinical experts on MM and myeloma bone disease developed these recommendations based on a review of evidence published

Table 1. Summary of Bisphosphonate Guidelines in Multiple Myeloma

Factor	NCCN[14]	ESMO[17]	ASCO[15]	Mayo[16]	IMWG Reply to Mayo[18]	EMN[19]
Patient population	Active or all other stages of myeloma	Stage III or relapsed disease receiving conventional-dose chemotherapy	Lytic disease (lytic destruction of bone or compression fracture of spine from osteopenia) on plain radiographs or imaging studies	All patients with lytic bone disease on plain radiographs	In addition to radiographs, other imaging studies (MRI, CT, PET/CT)	All patients with lytic bone disease on plain radiographs
	Adjunctive therapy for bone disease		Patients with osteopenia but no evidence of lytic bone disease based on normal plain radiograph or BMD measurements	Patients with osteopenia or osteoporosis on BMD studies		Patients with osteopenia or osteoporosis on BMD studies
						Patients receiving chemotherapy
Administration	IV	Oral or IV	Oral or IV	IV	Oral or IV	Oral or IV
PAM IV infusion time	N/A	N/A	At least 2 hours	At least 2 hours	N/A	2 to 4 hours
Duration/frequency	N/A	Long term	Monthly for 2 years	Monthly for 2 years After 2 years: Discontinue if CR or stable plateau phase Decrease to every 3 months if active disease	2 years After 1 year: Discontinue if CR or VGPR and no active bone disease Continue if < VGPR and/or ongoing active bone disease After 2 years: Discontinue if no active bone disease If active bone disease, continue at own discretion	2 years, if not in CR After 1 year: Continue at physician discretion, if CR Restart on relapse
Monitoring	Chronic users should be monitored for renal function and ONJ	N/A	Monitor serum creatinine before each PAM or ZOL dose	N/A	N/A	Monitor patients for compromised renal function (creatinine clearance)
	Smoldering/stage I MM: Use BP in trial with yearly bone surveys		Regularly monitor serum calcium, electrolytes, phosphate, magnesium, hematocrit/hemoglobin			Patients with compromised renal function should have creatinine clearance rates, serum electrolytes, and albuminuria monitored
Choice	PAM or ZOL	N/A	ZOL, PAM, or CLO (non–United States)	PAM (favorable) or ZOL	PAM, ZOL, or CLO	ZOL, PAM, or CLO (where indicated)

Abbreviations: ASCO, American Society of Clinical Oncology; BMD, bone mineral density; BP, bisphosphonate; CLO, clodronate; CR, complete response; CT, computed tomography; EMN, European Myeloma Network; ESMO, European Society for Medical Oncology; IMWG, International Myeloma Working Group; IV, intravenous; MM, multiple myeloma; MRI, magnetic resonance imaging; N/A, not applicable; NCCN, National Comprehensive Cancer Network; ONJ, osteonecrosis of the jaw; PAM, pamidronate; PET, positron emission tomography; VGPR, very good partial response; ZOL, zoledronic acid.
Adapted with permission.[19]

Table 2. Levels of Evidence and Grades of Recommendations

Level/Grade	Description
Level of evidence	
I	Evidence obtained from meta-analysis of multiple well-designed, controlled studies; randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade of recommendation	
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV, and findings are generally consistent
C	There is evidence of types II, III, or IV, but findings are inconsistent
D	There is little or no systematic empirical evidence

in randomized clinical studies, meta-analyses, systematic reviews of published clinical studies, observational studies, and case reports through August 2012. Expert consensus was used to propose additional recommendations in situations where there were insufficient published clinical data. Levels of evidence and grades of recommendations were assigned using established criteria (Table 2). The recommendations were initially circulated in draft form to each panel member, who had an opportunity to comment on the levels of evidence as well as the systematic grading of clinical data supporting each recommendation. The manuscript subsequently underwent rounds of revision until consensus was reached by all authors.

GUIDELINE RECOMMENDATIONS: BPs

PATIENT POPULATION AND CHOICE OF BP

Recommendations

BPs should be initiated in patients with MM, with (grade A) or without (grade B) detectable osteolytic bone lesions on conventional radiography, who are receiving antimyeloma therapy as well as patients with osteoporosis (grade A) or osteopenia (grade C) resulting from myeloma. The beneficial effect of zoledronic acid (ZOL) in patients without detectable bone disease by magnetic resonance imaging (MRI) or positron emission tomography/computed tomography is not known.

Intravenous (IV) ZOL and pamidronate (PAM) exhibit comparable efficacy in reducing SREs in patients with MM and are recommended for preventing SREs in patients with active MM (grade A). IV ZOL is recommended over oral clodronate (CLO) because it is significantly more efficacious in preventing SREs (grade A).

ZOL rather than CLO is recommended in patients with newly diagnosed MM and bone disease at diagnosis because of its potential antimyeloma effects and survival benefits (grade A). ZOL is the only BP shown to increase survival in the whole studied population of a prospective randomized trial. Clinical outcomes in patients with MM who are not eligible for transplantation may also benefit from combining ZOL with antimyeloma therapy (grade B).

BPs are recommended for those with low- and intermediate-risk asymptomatic MM (AMM) if osteoporosis is identified by dual-energy x-ray absorptiometry scan in doses used in patients with osteoporosis (grade C). For high-risk AMM, or if one cannot differentiate between MM-related versus age-related bone loss, the treating physician should consider using dosing and schedule of BPs as with symptomatic MM, especially in patients with abnormal MRIs (grade D; panel consensus).

BPs are recommended for the treatment of osteoporosis in MGUS in doses used for patients with osteoporosis (grade C). Dual-energy x-ray absorptiometry scan should be considered for patients with MGUS because of their reported increase in SREs compared with age-matched controls (grade B).

For patients with a solitary lytic lesion and no evidence of osteoporosis, BP therapy is not indicated. If osteoporosis is present, BPs should be administered as for osteoporosis patients. If multiple lesions are present on MRI, the patient has MM bone disease and should be treated with monthly IV BPs (grade C; panel consensus).

IV ZOL or PAM or oral CLO can be used to control bone pain associated with myeloma bone disease (grade B). PAM 30 and 90 mg have shown comparable effects for preventing SREs (grade B).

Evidence

Patients with symptomatic MM. Several studies have evaluated the effects of BPs on SREs and bone pain in patients with MM (Table 3). Ibandronate is ineffective in reducing SREs or improving bone pain in patients with MM.[29] The oral BP, CLO, reduced the proportion of patients with MM who experienced progression of osteolytic lesions by 50% compared with placebo (24% *v* 12%; $P = .026$)[23] and reduced the time to first nonvertebral fracture and the rate of nonvertebral fracture (6.8% *v* 13.2% for placebo; $P = .04$) in patients with newly diagnosed MM.[13] Administration of oral PAM failed to reduce SREs relative to placebo.[26] However, administration of IV PAM to patients with myeloma with at least one osteolytic lesion resulted in a significant reduction in SREs (24%) versus placebo (41%; $P < .001$). Patients receiving PAM also experienced reduced bone pain and no deterioration in QoL during the 2-year study.[27] A recent study in patients with newly diagnosed MM ($N = 504$) demonstrated that PAM 30 mg monthly had comparable time to SREs and SRE-free survival time compared with PAM 90 mg. Patients received PAM for at least 3 years, and patients receiving PAM 30 mg showed a trend

Table 3. Large Controlled Studies of BP Therapy in Multiple Myeloma

Controlled Trial	Year	BP	Dosage	MM (No. of patients)	Reduction of SREs*	Survival Benefit
Placebo						
Lahtinen et al[23]	1992	CLO	2.4 g per day orally for 2 years	350	Yes	NE
Laakso et al[24]	1994					
McCloskey et al[13]	1998	CLO	1.6 g per day orally	530	Yes	Subset†
McCloskey et al[25]	2001					
Brincker et al[26]	1998	PAM	300 mg per day orally	300	No	No
Berenson et al[27]	1996	PAM	90 mg IV every 4 weeks for 21 cycles	392	Yes	Subset‡
Berenson et al[28]	1998					
Menssen et al[29]	2002	IBN	2 mg IV once per month	198	No	No
PAM, 90 mg						
Gimsing et al[30]	2010	PAM	30 *v* 90 mg IV every 4 weeks	504	Comparable	No change
Berenson et al[31]	2001	ZOL	2 or 4 mg IV once per month	108	Yes	NE
Rosen et al[32]	2001	ZOL	4 or 8 mg IV once per month	513	Yes	Subset§
Rosen et al[33]	2003					
CLO, 1.6 g						
Morgan et al[34]	2010	ZOL	4 mg IV every 3 to 4 weeks	1,960	Yes	Yes
Morgan et al[35]	2011					
Morgan et al[36]	2012					

NOTE. Data adapted.[19,30,34]

Abbreviations: BP, bisphosphonate; CLO, clodronate; IBN, ibandronate; IV, intravenous; MM, multiple myeloma; NE, not evaluated; PAM, pamidronate; SRE, skeletal-related event; ZOL, zoledronic acid.

*SREs include vertebral and nonvertebral fractures, need for radiation or surgery to bone, spinal cord compression.

†In post hoc analysis, patients without vertebral fracture at study entry survived significantly longer with CLO (median survival, 23 months) compared with placebo.

‡Survival in patients with more advanced disease was significantly increased in the PAM group (median survival, 21 *v* 14 months; $P = .041$, adjusted for baseline serum β_2-microglobulin and Eastern Cooperative Oncology Group performance status).

§Survival benefit with ZOL over PAM in subgroup of patients who had elevated baseline bone-specific alkaline phosphatase levels.

toward lower risks of osteonecrosis of the jaw (ONJ) and nephrotoxicity relative to PAM 90 mg.[30] However, the study was not powered to show SRE differences between the two PAM dosages but only to show QoL differences.

ZOL was at least as effective as PAM in reducing the incidence of SREs and pain and delaying the time to first SRE in patients with MM in the conventional chemotherapy era.[31-33] The recent Medical Research Council Myeloma IX (MRC-IX) study (N = 1,960) demonstrated that a significantly smaller proportion of patients with newly diagnosed MM receiving ZOL versus oral CLO in addition to first-line antimyeloma therapy developed SREs before progression (27.0% *v* 35.3% for CLO; $P < .001$).[34,35] ZOL reduced the risk of SREs by 26% relative to CLO (hazard ratio [HR], 0.74; $P < .001$). Reduction in the risk of any SRE was evident in ZOL-treated patients with (HR, 0.774; $P = .0038$) and without (HR, 0.53; $P = .0068$) bone lesions at baseline over CLO-treated patients. This is the first time that a BP showed a reduction in SREs in patients with myeloma who required therapy and had no bone disease, assessed by conventional radiography at baseline.[35] Furthermore, ZOL significantly reduced the risk of SREs versus CLO regardless of whether patients received thalidomide maintenance.[36]

The MRC-IX study also demonstrated that addition of ZOL to standard first-line antimyeloma therapy reduced the risk of death by 16% ($P = .012$) and prolonged median overall survival (OS) by 5.5 months (50 *v* 44.5 months) and median progression-free survival by 2 months (19.5 *v* 17.5 months) over CLO.[34] In subset analyses, the OS advantage with ZOL over CLO was observed only in patients with bone disease at baseline (HR, 0.82; $P = .0107$).[36] However, it is important to mention that the multiple unplanned subanalyses of the MRC-IX study were a concern for several members of the group.

Other BPs have been also associated with improved survival in subsets of patients. Patients receiving second-line antimyeloma chemotherapy and treated with PAM experienced a borderline improvement in OS over placebo (Table 4),[28] whereas CLO had an OS advantage in patients without vertebral fractures at presentation relative to placebo.[25] A recent meta-analysis showed that ZOL was the only BP associated with superior OS compared with placebo (HR, 0.61; 95% CI, 0.28 to 0.98) but not compared with other BPs.[37]

Patients with AMM. IV PAM (60 to 90 mg monthly for 12 months) in patients with AMM reduced bone involvement at progression but did not decrease the risk or increase the time to progression.[38] Similarly, IV ZOL (4 mg monthly for 12 months) reduced the SRE risk at progression but did not influence the risk of progression in patients with AMM.[39]

Several studies have reported the value of MRI (presence of > one focal lesion and presence of diffuse pattern of marrow infiltration) in detecting patients with AMM at high risk for progression.[40,41] Because there are no data supporting progression-free survival advantage with BPs in AMM, BPs should not be recommended except in a clinical trial of high-risk patients.

Patients with MGUS. Patients with MGUS are at high risk for developing osteoporosis and pathologic fractures.[42,43] Three doses of ZOL (4 mg IV every 6 months) increased bone mineral density (BMD) by 15% in the lumbar spine and by 6% in the femoral neck in patients with MGUS with osteopenia or osteoporosis.[44] Oral alendronate (70 mg weekly) also increased BMD of the lumbar spine and total femur by 6.1% and 1.5%, respectively, in 50 patients with MGUS with vertebral fractures and/or osteoporosis.[45]

Patients with solitary plasmacytoma. Patients with solitary plasmacytoma and no evidence of MM do not require therapy with BPs.

Table 4. Clinical Outcomes in Patients With Multiple Myeloma Treated With Bisphosphonate Therapy

Study	Year	Patient Population	Treatment	Overall Survival				Progression-Free Survival			
				Median (months)	HR	95% CI	*P*	Median (months)	HR	95% CI	*P*
Morgan et al (MRC Myeloma IX)[34]	2010	Newly diagnosed patients with MM	ZOL (n = 981)	50	0.842	0.74 to 0.96	.012	19.5	0.883	0.80 to 0.98	.018
			CLO (n = 979)	44.5				17.5			
Berenson et al[28]	1998	Patients with MM who received second-line antimyeloma chemotherapy (stratum two)	PAM (n = 66)	21		N/A	.081	N/A		N/A	N/A
			PLA (n = 65)	14							
McCloskey et al[25]	2001	Patients with no vertebral fractures at presentation	CLO (n = 73)	59	0.62	0.43 to 0.87	.004	N/A		N/A	N/A
			PLA (n = 80)	37							

Abbreviations: CLO, clodronate; HR, hazard ratio; MM, multiple myeloma; MRC, Medical Research Council; N/A, not applicable; PAM, pamidronate; PLA, placebo; ZOL, zoledronic acid.

However, these patients should undergo whole body MRI, because in a study of 17 patients diagnosed with a solitary plasmacytoma, all showed additional focal lesions or diffuse infiltration on MRI, leading to classification as stage I MM (76%), stage II MM (12%), or stage III MM (12%) using the Durie-Salmon Plus system.[46]

ROUTE OF ADMINISTRATION

Recommendations

IV administration of BPs is the preferred choice (grade A). Home IV infusion or oral administration may be considered for patients who cannot receive hospital care (grade D).

Evidence

Strict adherence to dosing recommendations is required for BP therapy to effectively reduce and delay SREs in patients with MM. Each patient prescribed BP therapy should be instructed about the crucial importance of adherence to the dosing regimen. Although a few randomized, placebo-controlled clinical studies have suggested that long-term compliance with oral BPs such as CLO is satisfactory in patients with MM,[13,23] compliance with oral BP therapy is generally suboptimal.[47] Furthermore, the MRC-IX data strongly support the use of IV ZOL over CLO in all outcomes measured, including reduction of SREs and improvement in OS.[34-36] However, oral administration remains an option for patients who cannot receive regular hospital care or in-home nursing visits.

Administration of IV BPs such as ZOL or PAM is generally performed as an outpatient procedure in a clinical environment but may also be performed at home.[48] Routine patient monitoring can be combined with the administration of the IV infusion. Infusion times range from 15 minutes for ZOL to 2 to 4 hours for PAM. One study reported that 92% of patients preferred ZOL over PAM because of the shorter infusion time.[49]

TREATMENT DURATION

Recommendations

IV BPs should be administered at 3- to 4-week intervals to all patients with active MM (grade A). ZOL improves OS and reduces SREs over CLO in patients who received treatment for more than 2 years; thus, it should be administered until disease progression in patients not achieving complete response (CR) or very good partial response (VGPR) and further continued at relapse (grade B). There is not similar evidence for PAM. PAM may be continued in patients with active disease at the physician's discretion (grade D), and PAM therapy should be resumed after disease relapse (grade D). For patients in CR or VGPR, the optimal treatment duration of BPs is not clear; the panel agrees that BPs should be administered for at least 12 months and up to 24 months and then at the physician's discretion (grade D; panel consensus). Because of higher reported rates of ONJ with extended duration of therapy, discontinuation of ZOL or PAM may be considered after 1 to 2 years in patients who have achieved CR or VGPR (grade D; panel consensus).

Evidence

Until data from the Bismarck and other trials using bone resorption markers to dictate dosing frequency are available, IV BPs should be administered every 3 to 4 weeks, as per previous guidelines.[15,19] The subanalyses of the MRC-IX study showed that among patients who received at least 2 years of BP therapy (n = 582), ZOL reduced the incidence of SREs versus CLO (log-rank $P = .0102$). More importantly, in the same group of patients, ZOL improved OS from initial random assignment (median not reached; HR, 0.60; $P = .02$) and after first disease progression event versus CLO (34 *v* 27 months, respectively; HR, 0.58; $P = .03$).[36] The panel supports the use of ZOL beyond 2 years and until disease progression for patients not in CR or VGPR, because there are no data for survival or SRE advantage among patients achieving CR or VGPR. Indeed, the continuation of BPs in these patients is an important issue, because novel agent–based therapies have increased the CR/VGPR rate. A French study showed that PAM alone as a maintenance therapy did not reduce SREs and had no survival benefit compared with thalidomide alone in patients undergoing autologous stem-cell transplantation after a median time of 29 months.[50] The CR/VGPR rate in this study was more than 55% in all treatment arms. However, none of these patients received PAM before its use as maintenance.[50] Another small retrospective study in 44 patients with myeloma who were in sustained remission after antimyeloma therapy for more than 2 years showed an increase in lumbar spine BMD progressively after a mean follow-up of 3 years; these patients did not receive BPs, and thus, the BMD increase was related to the sustained response to antimyeloma treatment.[51] For these reasons, BP therapy has been tested at a reduced dose or longer intervals,[30,52] without the drawing of final conclusions because of limitations of these studies.

ADVERSE EVENTS

Recommendations

Clinicians should ask their patients about symptoms suggesting adverse events (AEs) and should monitor their patients for the development of more serious complications. Patients should also be instructed on how to recognize AEs and on the importance of early reporting (panel consensus).

Calcium and vitamin D3 supplementation should be used to maintain calcium homeostasis (grade A). Calcium supplementation should be used with caution in patients with renal insufficiency. All BP-treated patients should have creatinine clearance (CrCl), serum electrolytes, and urinary albumin monitored (grade A).

Preventive strategies should be adopted to avoid ONJ. Patients should receive a comprehensive dental examination and be educated regarding optimal dental hygiene (grade C; panel consensus). Existing dental conditions should be treated before initiating BP therapy (grade C; panel consensus).

After BP treatment initiation, unnecessary invasive dental procedures should be avoided, and dental health status should be monitored on at least an annual basis (grade C). Patients' ongoing dental health status should be monitored by a physician and dentist (grade D; panel consensus). Dental problems should be managed conservatively, if possible (grade C). Temporary suspension of BP treatment should be considered if invasive dental procedures are necessary (grade D). The panel consensus is to stop BPs for 90 days before and after invasive dental procedures (eg, tooth extraction, dental implants, and surgery to the jaw). BPs do not need to be discontinued for routine dental procedures, including root canals.

Initial treatment of ONJ should include discontinuation of BPs until healing occurs (grade C). The decision to restart BPs should be

made on an individual basis until the results of prospective long-term studies are available (grade D). The physician should consider the advantages and disadvantages of continued treatment with BPs, especially in the relapsed/refractory MM setting (grade D).

Evidence

BP therapy is generally well tolerated in patients with MM. Potential AEs associated with BP administration include hypocalcemia and hypophosphatemia, GI events after oral administration, inflammatory reactions at the injection site, and acute-phase reactions after IV administration of amino BPs. Renal impairment and ONJ represent infrequent but potentially serious AEs with BP use.

Hypocalcemia is usually relatively mild and asymptomatic with BP use in most patients with MM. The incidence of symptomatic hypocalcemia is much lower in those with MM compared with patients with solid tumors. Although severe hypocalcemia has been observed in some patients,[53] these events are usually preventable via the administration of oral calcium and vitamin D3. Patients should routinely receive calcium (600 mg per day) and vitamin D3 (400 IU per day) supplementation; 60% of patients with MM are vitamin D deficient or insufficient.[54,55] Because vitamin D deficiency increases bone remodeling, particularly parathyroid hormone levels, it is important that patients be calcium and vitamin D sufficient.[56] Calcium supplementation should be used with caution in patients with renal insufficiency.

BP infusions are associated with both dose- and infusion rate–dependent effects on renal function. The potential for renal damage is generally dependent on the concentration of BP in the bloodstream, and the highest risk is observed after administration of high dosages or rapid infusion. Both ZOL and PAM have been associated with acute renal damage or increases in serum creatinine.[27,32-34,36,57-60] Patients should be closely monitored for compromised renal function by measuring CrCl before administration of each IV BP infusion. Patients with mild to moderate renal impairment, defined by a CrCl rate of 30 to 60 mL/min, should receive reduced doses of CLO and ZOL under close clinical monitoring, as previously recommended.[19] No change to ZOL infusion time is recommended. PAM should be administered via extended infusion duration ($>$ 4 hours), and clinicians should also consider reducing the initial dose in patients with renal impairment. PAM and ZOL are not recommended for patients with CrCl $<$ 30 mL/min.

Early diagnosis is crucial, and urinary albumin and serum electrolytes in addition to CrCl rates should be monitored in these patients. Oral CLO is contraindicated if CrCl is $<$ 12 mL/min. Adherence to recommended infusion protocols regarding dosage, infusion time, serum creatinine levels, and hydration is mandatory to minimize the potential for renal damage. BP therapy should be discontinued in patients experiencing renal problems until serum creatinine levels return to within 10% of baseline values.

ONJ, characterized by exposed bone in the mouth that does not heal with 6 to 8 weeks of therapy, is a potentially serious complication of BP therapy. Retrospective studies have suggested that 4% and 11% of patients develop ONJ.[61,62] ZOL has been associated with a higher reported rate of ONJ than other BPs, and the cumulative dose and duration of therapy are believed to contribute to the development of ONJ.[61,62] In the MRC-IX study, the ONJ incidence with ZOL was approximately 1% per year (5% at a median follow-up of 4.8 years); these patients did not receive mandatory dental prophylaxis as part of this trial.[34,36] Among patients who received ZOL beyond 2 years, 4.1% developed ONJ.[36] In another prospective study comparing ZOL with denosumab in patients with solid tumors and bone metastases or with MM (10% of the population studied), the incidence of ONJ after 2 years was 1.3% with ZOL and 1.1% with denosumab.[59] Additional risk factors for ONJ include dental procedures, local infections, and treatment with corticosteroids.[61-63] The implementation of appropriate preventive measures greatly reduced the number of ONJ cases.[64-66] Clinical studies support restarting BP therapy after healing of ONJ. A long-term follow-up study of 97 patients with MM with ONJ demonstrated that patients who developed ONJ after dental procedures were less likely to have recurrence or nonhealing lesions after BP reinitiation upon healing of ONJ compared with patients who developed spontaneous ONJ.[63] Recurrence of ONJ was linked to rechallenge with BP therapy, mainly in the relapsed setting.[63]

KYPHOPLASTY AND VERTEBROPLASTY

Recommendations

Balloon kyphoplasty (BKP) should be considered for symptomatic vertebral compression fractures (VCFs) and is the procedure of choice to improve QoL in patients with painful VCFs (grade A). The role of vertebroplasty for patients with myeloma is less clear, because there are no randomized trials of vertebroplasty among patients with myeloma.

Evidence

Several studies have demonstrated that BKP and vertebroplasty are well-tolerated and effective procedures that provide pain relief and improve functional outcomes in patients with painful neoplastic spinal fractures. A single randomized study of 134 patients with bone metastases resulting from solid tumors and MM demonstrated that treatment of VCFs with BKP was associated with clinically meaningful improvements in physical functioning, back pain, QoL, and ability to perform daily activities relative to nonsurgical management. These benefits persisted throughout the 12-month study.[67] A meta-analysis of seven nonrandomized studies of patients with MM or osteolytic metastasis revealed that BKP was associated with reduced pain and improved functional outcomes, benefits that were maintained up to 2 years postprocedure ($N = 306$). BKP also improved early vertebral height loss and spinal deformity, but these effects were not long term[68] (Table 5). Similarly, a retrospective review of 67 patients with MM-related VCFs demonstrated that vertebroplasty provided clinically meaningful improvements in physical functioning, pain, and mobility throughout 12 months of follow-up.[75] Several small nonrandomized studies of BKP or BKP and vertebroplasty have generated comparable results.[76-78] However, the role of vertebroplasty for patients with myeloma remains debatable in the absence of prospective data,[77,79] because two randomized trials failed to show any benefit with vertebroplasty in patients with osteoporotic fractures versus conservative therapy.[80,81] Furthermore, a meta-analysis of 59 studies (56-case series) showed that BKP seemed to be more effective than vertebroplasty in relieving pain secondary to cancer-related VCFs and was associated with lower rates of cement leakage.[82]

Table 5. Efficacy of Balloon Kyphoplasty for Malignant Spinal Fractures: Results of a Meta-Analysis

Variable	No. of Studies	No. of Patients or Levels	Size of Effect	95% CI	*P*	I^2 (%)
Pain: VAS score (0-10)						
Basal (postoperative)	4[69-72]	172 patients	SMD: 3.85	2.99 to 4.71	< .001	79
Baseline (end of follow-up)	3[70-72]	109 patients	SMD: 4.27	2.38 to 6.21	< .001	93
Functional capacity: ODI (0-100)						
Baseline (postoperative)	4[69,71,72]	173 patients	WMD: −28.78	−11.5 to −46.0	.001	99
Baseline (< 6 months)	2[69,73]	82 patients	WMD: −16.39	−14.25 to −18.5	.001	0
Baseline (2 years)	2[71,72]	91 patients	WMD: −41.95	−39.42 to −44.5	.001	0
Kyphotic deformity: Cobb angle						
Basal (postoperative)	3[71,72,74]	180 levels	SMD: −0.69	−0.20 to −1.16	.001	78
Baseline (end of follow-up)	3[71,72,74]	155 levels	SMD: −0.39	0.05 to −0.84	.08	74
Vertebral height	3[69,70,74]	342 levels	RR: 47%	33% to 61%		38
Percentage of restitution increase, mm	2[71,72]	158 levels				
Anterior vertebral body						
Basal (postoperative)			SMD: 0.28	0.06 to 0.51	.01	0
Baseline (end of follow-up)			SMD: 0.15	−0.16 to 0.45	.35	37
Midline vertebral body						
Basal (postoperative)			SMD: 0.28	0.003 to 0.56	.04	34
Baseline (end of follow-up)			SMD: 0.15	−0.17 to 0.46	.35	41

NOTE. All based on random effects meta-analysis. Reprinted with permission.[68]
Abbreviations: ODI, Oswestry Disability Index; RR, rate ratio; SMD, standardized mean difference; VAS, visual analogue scale; WMD, weighted mean difference.

RADIATION THERAPY

Recommendations

Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, impending pathologic fracture, or impending SCC. Upfront external beam radiation therapy should be considered for patients with plasmacytoma, extramedullary masses, and SCC (grade C). However, the use of radiotherapy for local disease control and palliation should be used judiciously and sparingly depending on patient's presentation, need for urgent response, and treatment history and prior response. It should be limited as much as possible to spare the patient's marrow function. Current novel agents work rapidly and should decrease the need for palliative radiotherapy.

Evidence

Several studies, a majority of which were retrospective and included relatively small patient cohorts, have demonstrated that radiotherapy provided pain relief, decreased analgesic use, promoted recalcification, reduced neurologic symptoms, and improved motor function and QoL in patients with MM.[83-85] In addition, the total administered dose should be limited and the field of therapy restricted, especially when the aim of treatment is pain relief rather than treatment or prevention of pathologic fractures. A single 8- to 10-Gy fraction is generally recommended. Indeed, single fractions are increasingly preferred to fractionated treatment. No difference in rapidity of onset or duration of pain relief was observed between a single 8-Gy fraction and a fractionated 2-week course of 30 Gy in a randomized study of 288 patients with widespread bony metastases, including 23 patients with MM.[86]

MM accounts for 11% of the most-prevalent cancer diagnoses causing SCC.[87] In the largest retrospective series to date, radiotherapy alone improved motor function in 75% of patients with MM and SCC. One-year local control was 100%, and one-year survival was 94%.[88]

SURGERY

Recommendations

Orthopedic consultation should be sought for impending or actual long-bone fractures, bony compression of the spinal cord, or vertebral column instability (grade D). Consideration and indications for surgery should occur in consultation with the treating oncologist/hematologist and the orthopedic and neurosurgeon to determine when MM treatment can be safely restarted.

Evidence

Surgery is usually directed toward preventing or repairing axial fractures, unstable spinal fractures, and SCC in patients with myeloma. Decompression laminectomy is rarely required in those with

Table 6. New Recommendations for Use of Bisphosphonates in Multiple Myeloma

Factor	Recommendation
Patient population	Newly diagnosed patients with MM who require antimyeloma treatment (regardless of bone status)
Administration	IV
Duration/frequency	Monthly during initial therapy and ongoing in patients who are not in remission
	After 2 years, discontinue if CR/VGPR; continue if ≤ PR
Monitoring	Monthly creatinine clearance
Choice	ZOL (first option)
	PAM (second option)
	CLO (only in patients who cannot come to hospital, those with severe disabilities, and those with contraindications to ZOL and PAM)

Abbreviations: CLO, clodronate; CR, complete response; IV, intravenous; MM, multiple myeloma; PAM, pamidronate; PR, partial response; VGPR, very good partial response; ZOL, zoledronic acid.

MM, but radioresistant MM or retropulsed bone fragments may require surgical intervention.[89] In a relatively large study, 75 patients with MM were treated surgically (83 interventions) for skeletal complications of the disease. Most of the lesions were in the axial skeleton or the proximal extremities, apart from one distal lesion of the fibula, and most surgery was performed in the spine (35 patients). Surgical treatment in these patients was mostly limited to a palliative approach and was well tolerated.[90]

DISCUSSION

BPs are recommended in all patients with MM requiring front-line therapy, regardless of the presence of bone disease at diagnosis, assessed by conventional radiography. Although ZOL, PAM, and CLO reduce SREs and control bone pain compared with placebo, ZOL is associated with improved survival in patients with newly diagnosed MM and bone disease and reduces SREs over CLO. This benefit remains in patients who receive ZOL for more than 2 years. Therefore, ZOL should be administered until disease progression, except in patients who have achieved CR or VGPR, for whom there are no data regarding the survival advantage of ZOL. For PAM, there are no data demonstrating a survival advantage; it can be administered up to 2 years and continued at the physician's discretion in a patient with active myeloma. BP therapy is generally well tolerated, but preventive strategies should be adopted to avoid renal impairment or ONJ. Local radiotherapy should be considered for painful bone lesions and BKP for the treatment of VCFs (Table 6).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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